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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/460,216	12/13/1999	GRAHAM P. ALLAWAY	50875-F-PCT-	2202

7590 02/27/2003

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NEW YORK, NY 10036

EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	#16

DATE MAILED: 02/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Enclosed are the copies of the last Office Action, remailed, due to an incorrect address.

THE PERIOD FOR RESPONSE OF 03 MONTHS SET IN SAID OFFICE ACTION IS RESTARTED TO BEGIN WITH THE DATE OF THIS LETTER.

Carolyn E. Thomas,

Legal Instrument Examiner, Art Unit 1648

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/876,536	06/16/1997	URSULA ERHARDT	P60191US2	5121

7590 08/27/2002

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EXAMINER	
NGUYEN, BAO THUY L	

ART UNIT	PAPER NUMBER
1641	14

DATE MAILED: 08/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/460,216	ALLAWAY, G. P. ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

Status of the Claims

1. Acknowledgement is hereby made of receipt and entry of the amendment filed 08 April, 2002, wherein claim 65 was canceled without prejudice or disclaimer and claim 61 amended. Claim 61 is pending in the instant application.

Information Disclosure Statement

2. The information disclosure statement filed 13 June, 2002, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 61 stands rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim is broadly directed toward a method for inhibiting HIV-1 infection of $CD4^+$ cells through the administration of a non-peptidyl inhibitory agent that is capable of binding to a chemokine coreceptor required for viral entry.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation are

disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide any guidance pertaining to the structural requirements of any given non-peptidyl inhibitor that is not a bycyclam or derivative thereof. The disclosure fails to teach which chemical structures are critical for binding to any given chemokine coreceptor and which structures are critical for the antiviral activity. The disclosure fails to identify any parent compounds, or derivatives thereof, that can reasonably be expected to function in the desired manner. Thus, the skilled artisan has been extended an undue invitation to further experimentation to try to identify putative antiviral agents and determine their structures.

2) The disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating HIV-1 envelope/coreceptor/antiviral binding interactions. In order to rationally design a putative therapeutic, the skilled artisan would need a knowledge of those portions of CCR5 or CXCR4 that should be targets of any given antiviral. However, the specification is silent pertaining to this concern and fails to identify any critical regions of the chemokine coreceptors that should be the targets of antiviral development.

3) The disclosure fails to provide any working embodiments the meet the claimed limitations. While it is noted that the disclosure describes the identification of a putative antiviral agent (e.g., JM3100), nevertheless, this compound is a bycyclam agent and does not fall within the claimed limitations. There are no other examples involving non-peptidyl agents provided in the disclosure.

4) The claims are of excessive breadth and encompass any given putative antiviral agent without providing any meaningful structural limitations concerning that agent. The disclosure simply fails to support such breadth in the claim language.

5) The prior art describes a number of concerns pertaining to the development of fusion inhibitors. First, it is well-known that the chemokine family includes a large number of proteins that share limited genetic relatedness (~ 20%) (Proudfoot *et al.*, 1999; Proudfoot *et al.*, 2000). Thus, it appears unlikely that any given inhibitor will have a broad range of activity, particularly in the absence of the identification of any critical molecular determinants that are shared by all members of the family. Second, even if a putative antiviral compound was identified, there are a number of important immunological of therapeutic concerns that need to be considered (Berger *et al.*, 1999). For instance, will the loss of normal chemokine receptor function of a specific coreceptor be tolerated and accepted in the host? Will the impairment of CCR5 coreceptor usage accelerate disease progression by enhancing the selection for CXCR4 coreceptor usage? Do multiple members of the coreceptor repertoire need to be blocked in order to achieve a therapeutic effect? The disclosure is silent pertaining to these concerns.

6) The prior art (Öberg and Vrang, 1990; Yarchoan and Broder, 1992; Gait and Karn, 1995; Flexner and Hendrix, 1997) also provides a number of generic concerns pertaining to the development of any given putative antiviral compound to inhibit HIV-1 infection. It

has been well-documented in the prior art that the development of suitable HIV-1 therapeutics has been a long and arduous process, often ending in failure. This is due to a number of considerations such as a failure to understand the molecular determinants modulating many viral protein and host cell factor interactions, the failure of *in vitro* tissue culture studies and *in vivo* animal models to adequately predict clinical efficacy, the failure of many compounds to have acceptable pharmacological profiles, despite initial favorable *in vitro* and *in vivo* activities, and the failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The difficulties associated with developing efficacious anti-HIV-1 agents are best summarized by Gait and Karn (1995) who state (see Conclusions, p. 37):

> There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivities for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage.

The disclosure fails to provide sufficient guidance pertaining to these caveats.

Applicants traverse and submit that the claimed invention is fully supported by the disclosure. A declaration was provided by Dr. Tatjan Dragic under 37 C.F.R. § 1.132 to further support this assertion. Applicants' arguments and the declaration of Dr. Dragic have been carefully considered but are insufficient to overcome the

rejection. While the declaration provides a generic screening assay to identify putative non-peptidyl inhibitors of HIV, applicants are reminded that the claims are directed toward methods of inhibiting HIV-1 infection of a $CD4^+$ cell through the administration of a non-peptidyl agent. Accordingly the claims encompass *in vitro*, *in vivo*, and clinical applications. However, nothing in the disclosure leads the skilled artisan to any particular class of compounds. The specification fails to provide any guidance pertaining to the molecular determinants of any given inhibitor or class of inhibitors. The specification fails to identify any putative antiviral compounds that can reasonably be expected to function *in vivo* or in the clinic. Finally, nothing in the response or declaration provides any data or evidence demonstrating that obviates the large number of references cited which demonstrate how difficult it is for the skilled artisan to identify and develop novel antiviral agents. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

35 U.S.C. § 120

5. As previously set forth, Applicants' claim for domestic priority under 35 U.S.C. § 119(e) and 120 was acknowledged. However, the applications upon which priority is claimed fail to provide adequate support under 35 U.S.C. § 112 for claims 61 and 65 of this application. These earlier applications relied upon fail to provide adequate support for non-peptidyl inhibitory agents that are not of the bicylam family. Accordingly, for the purposes of applying prior art, the effective filing data of the instant application will be 12 December, 1998.

35 U.S.C. § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claim 61 stands rejected under 35 U.S.C. § 102(a) as being anticipated by Howard *et al.* (1998). This teaching describes a method for inhibiting HIV-1 infection of $CD4^+$ cells through the administration of a non-peptidyl agent (e.g., NSC 651016, a distamycin analog) that binds to a chemokine receptor (e.g., CCR5, CXCR4) and is not a bicyclam or a derivative thereof (see Results, pp. 8-10). This teaching clearly meets all of the claimed limitations. Applicants' amendment and arguments fail to obviate the rejection for the reasons of record clearly set forth above.

Finality of Office Action

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.**

Correspondence

9. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

10. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

22 August, 2002

James C. Housel 8/26/02

JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600